REMARKS

In the Office Action of May 14, 2003, Claims 1, 5 and 11 were rejected. No claim was allowed. In response, Claims 1, 5 and 11 are amended and new Claim 12 is added to the application. Reexamination and reconsideration are respectfully requested in view of the foregoing amendments and the following remarks.

Rejection of Claims 1, 5 and 11 under 35 U.S.C. §112, first paragraph

Claims 1, 5 and 11 were rejected under 35 U.S.C. 112, first paragraph. on the alleged grounds that the specification, while being enabling for the production of histidine with a specific strain of *Escherichia coli*, i.e., strain H-9341, does not reasonably provide enablement for the production of this amino acid with any strain of microorganism resistant to 150 mg/l of an aminoquinoline or even a strain of *Escherichia* resistant to this amount of primaquine. The Examiner alleges that the specification does not enable a person skilled in the art to practice the invention commensurate in scope with the claims.

The Examiner takes the position that strain *E. coli* H-9341, which was obtained by random NTG mutagenesis and selection of strain *E. coli* ATCC 21318 requiring methionine, is the only strain enabled by the present specification for the production of histidine as claimed. The Examiner alleges that it would require undue experimentation for one skilled in the art to determine which other strains of microorganisms or of *Escherichia* would be suitable for the claimed invention, in view of the diversity of strains encompassed by "microorganism", since the term "microorganism" encompasses not only bacteria, but also fungi, yeasts, viruses, protozoa and plant and animal cells. In addition, the Examiner notes that a specific strain of *E. coli* was

mutagenized in order to obtain a histidine-producing strain having the required capability. The Examiner further alleges that there is no clear correlation between resistance to 150 mg/l of an aminoquinoline for any microorganism or even for strains of Escherichia and the production of histidine as required and that undue experimentation would be required to practice the invention as claimed due to the quantity of experimentation to screen and select microorganisms or *Escherichia* strains capable of producing histidine upon resistance to 150 mg/l of an aminoquinoline or even a strain of *Escherichia* resistant to this material; limited amount of guidance and limited number of working examples in the specification related to this screening and selection process to show the requisite correlation thereof, the unpredictable nature of the invention, and breadth of the claims.

In response, independent Claim 1 is amended to define the microorganism as belonging to the genus *Escherichia*. This amendment thus overcomes the Examiner's allegations that the "microorganism" in the claims encompasses not only bacteria, but also fungi, yeasts, viruses, protozoa and plant and animal cells. With respect to the Examiner's allegations that undue experimentation would be required to produce a microorganism belonging to the genus *Escherichia* having an ability to produce L-histidine and having resistance to 150 mg/l aminoquinoline derivative, Applicants provide a Declaration under 37 CFR 1.132 by Tetsuya Abe showing that microorganisms belonging to the genus *Escherichia* having resistance to 150 mg/l aminoquinoline derivative can be produced by straightforward steps of mutagenesis and selection as described in Example 1 of the specification and starting with *Escherichia* microorganisms other than H-9341. It is further shown that a microorganism so produced has a greater ability to produce L-histidine than a

microorganism that does not have resistance to 150 mg/l aminoquinoline derivative, thereby showing a correlation between resistance of an *Escherichia* microorganism to 150 mg/l of an aminoquinoline and the production of L-histidine. Accordingly, Applicants have shown that the teachings of the specification are enabling with respect to the amended claims and that the invention as defined in the claims can be practiced by persons skilled in the art without undue experimentation.

Withdrawal of the rejection of Claims 1, 5 and 11 under 35 U.S.C. 112, first paragraph, is therefore respectfully requested.

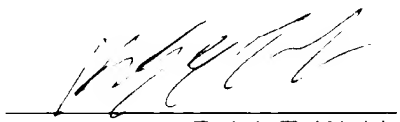
Conclusion

In view of the foregoing amendments and remarks, it is respectfully submitted that Claims 1, 5, 11 and 12 are in condition for allowance. Favorable reconsideration is respectfully requested.

Should the Examiner believe that anything further is necessary to place this application in condition for allowance, the Examiner is requested to contact applicants' undersigned attorney at the telephone number listed below.

Kindly charge any additional fees due, or credit overpayment of fees, to Deposit Account No. 01-2135 (506.39084X00).

Respectfully submitted,
ANTONELLI, TERRY, STOUT & KRAUS



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RTW/
(703)312-6600
Attachement: Declaration pursuant to
37 CFR 1.132 of Tetsuya Abe

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

K. KINO, ET AL.

Serial No. : 09/665,617

Filed: September 19, 2000

For:Method for producing amino acids by fermentation

At ty. Ref: 506. 39084XX0

Group: 1651

EXAMINER: Irene Marx

DECLARATION PURSUANT TO 37 C. F. R. 1.132

Sir:

I, Tetsuya Abe, of 4-17-9, Morino, Machida-shi, Tokyo 194-0022 Japan do hereby declare as follows,

I graduated from Division of Agricultural Chemistry, Faculty of Agriculture, Kyoto University, in March, 1992, and got a master's degree from Kyoto University in March, 1994. Since April, 1994, I have been employed by Kyowa Hakko Kogyo Co. Ltd. I was assigned to Technical Research Laboratories of the company in July, 1994, and was engaged in research and development of efficient fermentation production system.

I am one of the co-inventors of the invention described and claimed in the application and have a full knowledge of the present invention and cited references.

I conducted the following experiment to show that microorganisms belonging to Escherichia coli, having an ability to produce L-histidine and having resistance to 150mg/l primaquine disodium salt can be obtained other than Escherichia coli H-9341.

Experiment

<Methods>

Step 1

I obtained Escherichia coli H-9341(hereinafter referred to as H-9341 strain) and No.1 strain from Escherichia coli H-9340(hereinafter referred to as H-9340 strain) according to the process described in Example 1 of the present specification. The details are as follows.

H-9340 strain is a strain deposited on March 9, 1999 with the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan) under the Budapest Treaty with accession No. FERM BP-6673.

H-9340 strain was subjected to mutagenesis in an aqueous solution containing N-methyl-N'-nitro-N-nitrosoguanidine (NTG, 0.2 mg/ml) at 30°C for 30 minutes. Mutagenized cells were spread on an agar plate of the minimal medium containing 150 mg/l primaquine disodium salt. After 2 to 6 days of incubation at 30°C, about 500

colonies were appeared and 120 large colonies were picked up onto LB plates.

The picked up strains were transferred into test tubes containing 7 ml of a seed culture medium (2% glucose, 0.5% molasses, 1% corn steep liquor, 1.2% ammonium sulfate, 0.3% potassium dihydrogen phosphate, 0.015% magnesium sulfate, 600 mg/liter DL-methionine, 100 mg/liter adenine, 3% calcium carbonate, pH 6.2), and cultured at 30°C for 12 hours under aerobic condition with shaking. After completion of the culturing, 0.1 ml of each of the resulting seed culture was transferred into test tubes containing 5 ml of a production culture medium (6% glucose, 1% corn steep liquor, 2.4% ammonium sulfate, 0.4% potassium dihydrogen phosphate, 0.015% magnesium sulfate, 10 mg/liter thiamine chloride salt, 10 mg/liter calcium pantothenate, 3% calcium carbonate, pH 6.5), and cultured at 30°C for 48 hours under aerobic condition with shaking. After culturing, the amount of accumulated L-histidine in the culture was assayed by high-performance liquid chromatography. Among the strains thus cultured, H-9341 strain and the other strain (hereinafter referred to as strain No.1) were selected as strains having higher L-histidine productivity than H-9340 strain. The result of the culturing is shown in Table 1.

Step 2

Further, I obtained E. coli H-9343(hereinafter referred to as H-9343 strain) and No. 2 strain using a medium containing primaquine disodium salt from E. coli H-9342 strain(hereinafter referred to as H-9342 strain), as described below.

H-9342 strain is a strain deposited on March 9, 1999 with the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan) under the Budapest Treaty with accession No. FERM BP-6675.

H-9342 strain was subjected to mutagenesis in an aqueous solution containing NTG (0.2 mg/ml) at 30°C for 30 minutes. Mutagenized cells were spread on an agar plate of the minimal medium containing 150 mg/l primaquine disodium salt. After 2 to 6 days of incubation at 30°C, about 500 colonies were appeared and 120 large colonies were picked up onto LB plates.

The picked up strains were subjected to the culturing according to the same method as described in Step 1 above. After culturing, the amount of accumulated L-histidine in the culture was assayed by high-performance liquid chromatography. Among the strains thus cultured, H-9343 strain and No.2 strain were selected as strains having higher L-histidine productivity than H-9342 strain.

H-9343 strain was deposited on March 9, 1999 with the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan) under the Budapest Treaty with accession No. FERM BP-6676.

The result is shown in Table 2.

<Results>

Table 1

Bacterial strains	L-histidine(g/l)
H-9340	11.5
H-9341	14.2
No.1	14.0

Table 2

Bacterial strains	L-histidine(g/l)
H-9342	13.2
H-9343	16.0
No.2	15.4

As shown in Table 1, strain No.1, which was obtained as 150mg/l primaquine-resistant strains, produced L-histidine as well as H-9341. Further, as shown in Table 2, H-9343 and strain No.2, which were also obtained as 150mg/l primaquine-resistant strains, also produced L-histidine as well as or more than H-9341.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: This day of September 9, 2003.

Tetsuya Abe

Tetsuya Abe